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10/799,782	03/15/2004	Axel Ullrich	034536-1243	9104

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,782	ULLRICH ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Specification

The new title of the invention is acknowldeged.

In the previous Office Action, figures 11-1 to 11-4 were objected to because tables and sequence listings included in the specification must not be duplicated in the drawings. See 37 C.F.R. §1.58(a) and §1.83. Applicants have responded at page 4 of the amendment filed 10/12/2007 by stating that the sequences in the figures are *different* from those in the CRF. The brief description of the figures at page 8 of the specification does not recite any sequence identifier. Accordingly:

-The specification is objected to because the brief description of the figures refers to Figures 11A and 11B, and not figures 11-1 to 11-4.

-The specification is further objected to because the brief description of figures 11-1 to 11-4 does not refer to the sequences therein by SEQ ID NO: as required by 37 C.F.R. §1. 821.

-Having stated on the record that the sequences in figures 11-1 to 11-4 are *different*, the Examiner finds that the application is not in full compliance with sequence rules. Applicants are required to amend the specification to be in full compliance with sequence rules in response to this office action, and, if needed to submit a new CRF reflecting the different sequences, along with a new paper copy of the sequence listing and statement that the CRF and paper copy are identical, in addition to amending the specification to reflect the newly added sequence identifiers.

Appropriate correction is required.

Applicants are advised that figures 3-7 and 17 are of insufficient quality to convey any meaningful information. Applicants may desire to submit better copies of the figures prior to issuance of a patent.

The disclosure is objected to because of the following informalities:

In the amendment to the specification filed 10/12/2007 the word "entirety" should be deleted from the last line.

Appropriate correction is required.

The Abstract of the Disclosure is objected to because it is two paragraphs long. The abstract should be only a single paragraph of 150 words or less. Correction is *required*. See M.P.E.P. § 608.01(b). In the response filed 10/12/2007, applicants neglected to address this objection. Any further failure to address this objection will result in the response being found non-responsive.

Claim Interpretation

It is noted that the recitation in claims 5 and 6 of "cell line" is taken to indicate an *in vitro* cell population, and not to read on an animal or human.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-6 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,851,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-4 would be anticipated by the patented claims, as the claims are related as sub-genus to genus. With respect to claims 5 and 6, the person of ordinary skill in the art would immediately grasp, upon reading the patented claims, the desirability of making a cell line as currently claimed to produce the viral particles used in the patented pharmaceutical compositions. Accordingly, the claims are obvious over the patented claims.

Applicants intent to submit a terminal disclaimer is noted.3

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 remain rejected under 35 U.S.C. § 103 as being unpatentable over Lemischka, U.S. Patent Number 5,185,438, Matthews et al. (PNAS 88:9026) and Terman et al. (BBRC 187:1579), in view of Ullrich et al. (Cell 61:203), and Ueno et al., (Science 252:844, Ueno-1 and JBC 267:1470, Ueno-2), all references cited by applicants.

Applicants traversal in the response filed 10/12/2007 has been fully considered but is not deemed persuasive. At page 6 of the response, applicants argue that none of the primary references teaches a truncated Flk-I receptor within the metes and bounds of the claims, and that none of the secondary references teach elatedness to Flk-l. This argument has been fully considered but is not deemed persuasive because one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *111 re Keller,* 642 F.2d 413,208 USPQ 871 (CCPA 1981); *111 re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The primary references clearly teach the relatedness of Flk-1 to the receptors disclosed by the secondary references.

In response to applicant's implication at page 5 that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991).

Referring to the Ueno reference, applicants further argue that none of the references suggest that the truncated proteins are related to the Flk-1 receptor protein or that a truncated Flk-1 receptor protein would behave in a similar manner. This argument has been fully considered but is not deemed persuasive because as stated in the previous rejection, the remaining cited references (including two articles by Ueno), are all drawn to examples in which tyrosine kinase receptors structurally related to the Flk-1 receptor were altered within the cytoplasmic domain, resulting in proteins that formed signaling incompetent dimers, with dominant-negative characteristics. Based upon the structural similarity of Flk-1 to the c-Kit

family of receptors, and further in view of Ullrich et al. (Cell 61:203) who teach that although normal in its binding characteristics, the kinase-negative mutant of the EGF receptor was unable to stimulate calcium influx, inositol phosphate formation, Na+/H+ exchange, ..." , continuing "This suggests that all receptor tyrosine kinase signaling activities depend on a functional tyrosine kinase...". The person of ordinary skill in the art would expect a similar mutation in Flk-1 to retain at least normal binding activity, and to be signaling incompetent.

Applicants further argue unexpected results. These arguments are not persuasive, because the claimed cell line has exactly the properties expected. Applicants arguments are drawn to the methods of use of the protein encoded by the vector in the claimed cells, not to the use of the cells themselves, but of the protein encoded thereby. It remains that the cell line that produces the protein is obvious. The unexpected result that resulted in allowance of the method claims does not apply to the claimed cell lines, which comprise a nucleic acid that is obvious over the cited references, and which encodes a protein that has precisely the expected properties. It remains that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the nucleic acids and recombinant vectors of Matthews et al., Terman et al. or Lemischka to delete all or a portion of the sequence encoding the intracellular domain as taught by Ullrich and Ueno. The person of ordinary skill in the art would have been motivated to make such modifications in view of the teachings of Terman et al., specifically that Flk-1 is the murine homologue of the KDR receptor disclosed by Terman et al., and that it would be desirable to investigate the dimeric combinations in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand, VEGF (see teachings of Terman et al. as discussed above), and would further have been motivated by the teachings of Ullrich and Ueno that such deletions result in signaling incompetent receptors that act in a dominant-negative fashion *in vivo*, and that such results are expected to be generally applicable to tyrosine kinase receptors. The teachings of the secondary references would have provided further incentive to make such derivatives for the purpose of inhibiting the biological function of the receptor *in vivo*, which function was taught by Terman as being involved in angiogenesis. It would further have been obvious to incorporate such truncated coding sequences in a retroviral vector (and cell line containing such and producing

infectious particles) because retroviral vectors are known in the art to be useful for the efficient vectors for the introduction of DNA into eukaryotic cells.

The Examiner's position is supported by the recent finding by the Supreme Court in *KSR v. Teleflex, Inc.* (82 USPQ 2d 1385, 4/30/2007), which held that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103." (See 82 USPQ2d at 1397.) In this case, the art provides motivation to pursue the known option of making a deletion of Flk-1 for the purpose of making a signaling incompetent receptor in view of the Terman disclosure , and would have had a reasonable expectation of success.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1647